Remarks

Courtesies extended to Applicants' representative in the personal interview held on March 12, 2002, are acknowledged with appreciation.

The present invention provides methods for modulating expression of exogenous genes in cells containing a defined DNA construct. DNA constructs contemplated herein comprise an exogenous gene under the control of a (modified or unmodified) response element plus a modified ecdysone receptor which, in the presence of an appropriate ligand, binds to the response element. Optionally, a second receptor member is included that can act as a silent partner for the modified ecdysone receptor. The invention method comprises providing to a cell containing the construct an effective amount of a ligand(s) for the modified ecdysone receptor, wherein the ligand(s) is not normally present in the cell. The presence of ligand for the modified ecdysone receptor (and optionally, the presence of a receptor that can act as a silent partner) promotes the formation of ligand-receptor complexes that can interact with corresponding response elements, thereby modulating expression of exogenous genes.

Invention methods for modulating exogenous gene expression are useful in a wide variety of applications. Modulation of exogenous gene expression is desirable in numerous cell populations ranging from transiently modified cells to stably transformed cell lines. For example, invention methods can advantageously be employed in *in vitro* cellular expression systems to regulate expression of a recombinant expression product. Similarly, host cells and other recombinant cell types can benefit from invention methods for modulating the expression of an exogenous gene.

Claims 1-9, 11-13, 15-24, 39, 40 and 47-77 were pending before this response. By this response, claims 1, 3-6, 11, 19, 21-24, 50-52, 54, 55, 57-60, 64 and 66-77 have been amended to define Applicants' invention with greater particularity. In addition, claims 2 and 56 have been cancelled without prejudice. These amendments add no new matter as they are fully supported by the specification and the original claims. Attached hereto is a marked-up version of the changes made to the claims, labeled APPENDIX A.

Accordingly, claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55 and 57-77 are currently pending. For the Examiner's convenience, a clean copy of these claims is also provided in APPENDIX B.

The rejection of claims 1-9, 11-13, 15-24, 39, 40 and 47-77 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claims invention, is respectfully traversed. Applicants respectfully submit that in view of the specification, one would have no reason to doubt that Applicants had possession of the claimed methods for modulating gene expression. Applicants' method requires providing one or more ligands for a modified ecdysone receptor, which receptor can bind to a response element that controls expression of a gene. Each element of invention methods for modulating the expression of exogenous genes has been fully disclosed in the specification.

Applicants respectfully disagree with the Examiner's reading of the claims with respect to the response elements. Contrary to the Examiner's assertion that "the DNA construct comprising the exogenous gene is under the control of any and all response element(s)" (see Office Action at page 3, lines 1-3), it is clear that the claims embrace only those response elements that bind to the modified ecdysone receptor defined therein. For example, in claim 1, second clause (ii) clearly indicates that "the modified ecdysone receptor . . . binds to said response element", i.e. the response element of clause (i). Thus, the claims are not directed to DNA constructs comprising any and all response elements, but rather to response elements to which the modified ecdysone receptor binds.

In addition, claims 50, 67-71 and 75-77 specifically refer to an ecdysone response element, defined in detail in the specification as filed (see, for example, specification at page 31, line 16, through page 36, line 17). Accordingly, these claims do not embrace "any and all" response elements; rather they embrace only ecdysone response elements.

However, in order to expedite prosecution and to reduce the issues, all claims referring to "a response element" have been amended to specifically reference a response element to which a modified ecdysone receptor binds. Therefore, the specification provides adequate written description of the response element, and the claims embrace response elements clearly possessed by the Applicants at the time of filing.

Applicants further disagree with the Examiner's assertion that the claims comprise "any and all modified receptor(s) which in the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element" (see Office Action at page 3, lines 6-10). Contrary to the Examiner's assertion, independent claims 1, 22- 24 and 71-74 each explicitly refer to a modified ecdysone receptor, as defined in the specification as filed (see specification, for example, specification at page 12, line 9 through page 19, line 4).

The modified ecdysone receptor required by the claims is a chimeric receptor containing three mandatory domains: a ligand binding domain a DNA binding domain, and an activation domain. Each of these domains is further defined in the specification (see, for example, specification at page 12, line 32 through page 13, line 11, describing the ligand binding domain; at page 13, line 13 through page 14, line 2, describing the DNA binding domain; and at page 18, line 18 through page 19, line 4, describing the activation domains). Thus, the claims do not include any and all modified receptors. Rather, the claims require a specifically defined modified ecdysone receptor.

However, in order to expedite prosecution and to reduce the issues, claims 1, 22-24 and 71-74 have been amended to include descriptions of the three specific domains that comprise the chimeric modified ecdysone receptor. Similarly, claims 50, 67-70 and 75-77 also have been amended to include descriptions of the three specific domains that comprise the chimeric modified receptor. Therefore, all claims as amended embrace modified ecdysone receptors that are fully described in the specification and clearly possessed by the Applicants at the time of filing.

Moreover, Applicants respectfully submit that the Examiner's discussion regarding the dimer partners and dimerization of the native insect ecdysone receptor (see Office Action at page 4, lines 1-10) is irrelevant to Applicants' invention. As discussed during the personal interview, the invention modified ecdysone receptor, in contrast to the native ecdysone receptor, is capable of functioning as either a homodimer or a heterodimer. Thus, a silent partner, i.e., a receptor partner other than a modified ecdysone receptor, is optional. Accordingly, the claims refer to the optional presence of a silent partner for the modified ecdysone receptor.

The invention receptor is a modified ecdysone receptor composed of domains from various members of the steroid/thyroid hormone receptor superfamily. It is one of the benefits of the present invention that unique properties are imparted to the ecdysone receptor upon conversion into the chimeric modified receptor required by the present claims. Such unique properties include, for example, binding to or activation by elements other than the normal ecdysone system elements, and functional homodimerization. The state of the art supports the fact that a chimeric receptor according to the present invention is capable of homodimerization. For example, it was well known at the time of filing that chimeric GAL4-receptor constructs incorporating components from the steroid/thyroid receptor superfamily are capable of forming functional homodimers (see, for example, PCT/US94/14426). The specification clearly contemplates such homodimeric species of the modified ecdysone receptors, which do not require any dimer partner (see, for example, specification at page 20, line 36, through page 21, line 3). Thus, a heterodimer partner is clearly optional, and not a requirement of the present claims.

Applicants disagree with the Examiner's assertion that "the steroid/thyroid hormone superfamily receptors include members that would [be] expected to have widely divergent functional properties" (see Office Action at page 4, lines 23-25). Applicants also disagree with the Examiner's assertion that Applicants were not in possession of the claimed genus of modified ecdysone receptors because the art does not provide "any indication as how the structure of one receptor is representative of other unknown homologs having concordant or discordant

functions" (Office Action, page 5, lines 1-8). The Drosophila ecdysone receptor is a member of the well-defined steroid/thyroid hormone superfamily of receptors, which all operate as ligand-mediated transcription factors. It is specifically this functional capacity as gene regulators that is relevant to the present claims. Therefore, Applicants should not be limited to the exemplary species provided. Applicants respectfully submit that the exemplary species are fully representative of the genus because of the basic functional similarity among members of the superfamily.

In summary, Applicants have provided adequate written description of all elements required by the claims, and in view of the specification, one would have no reason to doubt that Applicants had possession of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

The rejection of claims 1-9, 11-13, 15-24, 39, 40 and 47-77 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for the method as claimed, is respectfully traversed. Applicants respectfully submit that the specification as filed enables any person skilled in the art to make and use the invention commensurate in scope with the present claims.

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The present invention methods, as defined by claim 1, require providing to an isolated cell an effective amount of one or more ligands not normally present in the cell, for a modified

ecdysone receptor. The cell contains a DNA construct composed of an exogenous gene under the control of a response element to which a modified ecdysone receptor binds; and a corresponding modified ecdysone receptor capable of binding in the presence of a ligand to the response element. One of skill in the art could readily follow the specific teachings of the specification to modulate expression of an exogenous gene as claimed.

With respect to the response element, as noted above, the claims clearly contemplate response elements to which modified receptors of the present invention can bind. Furthermore, the claims have been amended to further clarify the relationship between the response element and the modified receptor in each independent claim. In addition, the specification provides ample guidance to one of skill in the art regarding the ecdysone response element contemplated by invention methods (see specification, page 31, line 15 through page 36, line 26). Thus, the specification clearly enables the corresponding response elements.

Furthermore, with respect to the modified ecdysone receptor, also as noted above, the presence of a silent partner is optional, and the claims have been amended to include the specific components of the modified receptors claimed. Thus, contrary to the Examiner's assertion, one would not have to "characterize and modify any and all receptor[s] that regulates the expression of an exogenous gene operatively linked to any and all response elements containing any and all ligand binding domains, DNA-binding domains and activation domains" (see Office Action at page 8, lines 1-4). In contrast, the modified receptors of the present invention, which require specific domains as defined in the claims, is readily enabled by the teachings of the specification as filed, in light of methods known in the art (see specification, page 12, line 9 through page 19, line 4).

Applicants respectfully disagree with the Examiner's classification of claims 19-21 and 64-66 as being "in the realm of gene therapy" (see Office Action at page 8, lines 9-12). Claims 19-21 depend from claim 1, and claims 64-66 depend from claim 50. Both claims 1 and 50 explicitly require modulation of gene expression in an isolated cell. However, in order to expedite prosecution and reduce the issues, claims 19, 21, 64 and 66 have been amended as

discussed during the personal interview to delete reference to "a therapeutic gene". Claims 19, 21, 64 and 66 have been amended as suggested by the Examiner to require modulation of a "gene of interest".

Applicants further disagree with the Examiner's classification of claims 72-77 as being directed to gene therapy. The Examiner's arguments regarding the level of success of clinical trials are not relevant to the present claims because Applicants are not claiming methods of treatment or methods of curing diseases (see Office Action at page 8, line 12, through page 9 line 2). To the contrary, claims 72 and 75 are directed to methods for modulating the expression of an exogenous gene, and claims 73, 74, 76 and 77 are directed to methods of inducing the expression of an exogenous gene.

All that is required by Applicants' methods is a mammalian subject having a DNA construct containing an exogenous gene under the control of a response element to which a modified ecdysone receptor binds and a modified ecdysone receptor, as specifically described in the specification, and providing one or more ligands for the modified ecdysone receptor in an amount effective to modulate or induce the expression of the exogenous gene. Thus, one of skill in the art could readily follow the specific teachings of the specification to practice invention methods to modulate gene expression.

For all of the reasons cited above, it is respectfully submitted that the present invention is fully enabled as required by 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Conclsion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: May 20, 2002

Teresa Spehar
Registration No. 51,281
for Stephen E. Reiter
Registration No. 31,192
Telephone: (858) 847-6711
Facsimile: (858) 792-6773

Foley & Lardner
P.O. Box 80278
San Diego, CA 92138-0278

Enclosures: Appendices A and B

APPENDIX A – ALTERED CLAIMS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 3-6, 11, 19, 21-24, 50-52, 54, 55, 57-60, 64 and 66-77 have been amended as follows:

1. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of a response element **to which the modified ecdysone receptor of (ii) binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR); and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, **wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**;

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

3. (Amended) A method according to claim 1[2] wherein said modified ecdysone receptor is further characterized as having substantially no constitutive activity in mammalian cells.

4. (Amended) A method according to claim 1[2] wherein the DNA-binding domain of said modified ecdysone receptor is derived from a member of the steroid/thyroid hormone superfamily of receptors.

5. (Amended) A method according to claim 1[2] wherein said activation domain is obtained from a member of the steroid/thyroid hormone superfamily of receptors.

6. (Amended) A method according to claim 1[2] wherein said activation domain is a glucocorticoid receptor activation domain, a VP16 activation domain or a GAL4 activation domain.

11. (Amended) A method according to claim 1[47], wherein said receptor capable of acting as a silent partner is RXR.

19. (Amended) A method according to claim 1 wherein said exogenous gene is a wild type gene and/or [therapeutic] gene of interest.

21. (Amended) A method according to claim 19 wherein said [therapeutic] gene of interest encodes products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to cells in which they are expressed.

22. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising an exogenous gene under the control of a response element **to which the modified ecdysone receptor encoded by the DNA of (ii) binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR);

(ii) DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, **and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**; and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified ecdysone receptor.

23. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of a response element **to which a modified ecdysone receptor binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), said method comprising introducing into said cell:

a modified ecdysone receptor, **wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription**

factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said receptor, in combination with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, activating transcription therefrom.

24. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) a DNA construct encoding said recombinant product under the control of a response element **to which the modified ecdysone receptor encoded by the DNA of (ii) binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), and

(ii) DNA encoding a modified ecdysone receptor, **wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;**

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified ecdysone receptor, and optionally a receptor capable of acting as a silent partner for said modified ecdysone receptor.

50. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**;

said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

51. (Amended) A method according to claim **50[54]**, wherein said receptor capable of acting as a silent partner is **present [~~RXR~~]**.

52. (Amended) A method according to claim **51[54]**, wherein said receptor capable of acting as a silent partner is ultraspiracle.

54. (Amended) A method according to claim **51[50]**, wherein said receptor capable of acting as a silent partner is **RXR [~~present~~]**.

55. (Amended) A method according to claim **54[~~51~~]**, wherein said RXR is exogenous to said cell.

57. (Amended) A method according to claim **50**~~[56]~~ wherein said modified receptor is further characterized as having substantially no activity in mammalian cells.

58. (Amended) A method according to claim **50**~~[56]~~ wherein the DNA-binding domain of said modified receptor is derived from a member of the steroid/thyroid hormone superfamily of receptors.

59. (Amended) A method according to claim **50**~~[56]~~ wherein said activation domain is derived from a member of the steroid/thyroid hormone superfamily of receptors.

60. (Amended) A method according to claim **50**~~[56]~~ wherein said activation domain is a glucocorticoid receptor activation domain, a VP16 activation domain or a GAL4 activation domain.

64. (Amended) A method according to claim 50 wherein said exogenous gene is a wild type gene and/or ~~[therapeutic]~~ gene **of interest**.

66. (Amended) A method according to claim 64 wherein said ~~[therapeutic]~~ gene **of interest** encodes products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to cells in which they are expressed.

67. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;**

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified receptor.

68. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said cell:

a modified receptor, wherein said modified receptor has substantially no binding affinity for endogenous response elements, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a**

glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

wherein said modified receptor, in combination with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

69. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) a DNA construct encoding said recombinant product under the control of an ecdysone response element, and

(ii) DNA encoding a modified receptor, wherein said modified receptor has substantially no binding affinity for endogenous response elements**, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**; and

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified **[~~ecdysone~~]** receptor, and optionally a receptor capable of acting as a silent partner for said modified **[~~ecdysone~~]** receptor.

70. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element wherein said modified receptor has substantially no constitutive activity in mammalian cells, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**;

said method comprising providing to the cell an effective amount of one or more ligands for said modified [~~ecdysone~~] receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

71. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has an altered DNA binding specificity relative to the wildtype receptor from which it is derived, **and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an**

activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

72. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising said exogenous gene under the control of a response element **to which the modified ecdysone receptor of (ii) binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR); and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, **and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;**

said method comprising providing to said subject an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

73. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising an exogenous gene under the control of a response element **to which the modified ecdysone receptor encoded by the DNA of (ii) binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR);

(ii) DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, **and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**; and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified ecdysone receptor.

74. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of a response element **to which the modified ecdysone receptor described below binds**, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), said method comprising introducing into said subject:

a modified ecdysone receptor, **wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription**

factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said modified ecdysone receptor, in combination with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, activating transcription therefrom.

75. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising said exogenous gene under the control of an **ecdysone** [~~ecydsone~~] response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**;

said method comprising providing to said subject an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

76. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein**;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified receptor.

77. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said subject:

a modified receptor, wherein said modified receptor has substantially no binding affinity for endogenous response elements, **and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a**

glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

wherein said modified receptor, in connection with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

Claims 2 and 56 have been cancelled without prejudice.

APPENDIX B – COMPLETE SET OF PENDING CLAIMS

1. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of a response element to which the modified ecdysone receptor of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR); and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

3. (Amended) A method according to claim 1 wherein said modified ecdysone receptor is further characterized as having substantially no constitutive activity in mammalian cells.

4. (Amended) A method according to claim 1 wherein the DNA-binding domain of said modified ecdysone receptor is derived from a member of the steroid/thyroid hormone superfamily of receptors.

5. (Amended) A method according to claim 1 wherein said activation domain is obtained from a member of the steroid/thyroid hormone superfamily of receptors.

6. (Amended) A method according to claim 1 wherein said activation domain is a glucocorticoid receptor activation domain, a VP16 activation domain or a GAL4 activation domain.

7. A method according to claim 6 wherein said modified ecdysone receptor is VpEcR, VgEcR or GecR.

8. A method according to claim 7 wherein said modified ecdysone receptor is VgEcR having the amino acid sequence set forth in SEQ ID NO:5.

9. A method according to claim 1 wherein said modified ecdysone receptor is present primarily in the form of a homodimer.

11. (Amended) A method according to claim 1, wherein said receptor capable of acting as a silent partner is RXR.

12. A method according to claim 11 wherein said RXR is exogenous to said cell.

13. A method according to claim 1 wherein said response element is a modified response element which comprises, in any order, a first half-site and a second half-site separated by a spacer of 0-5 nucleotides;

wherein said first half-site has the sequence:

-RGBNNM-,

wherein

each R is independently selected from A or G;

each B is independently selected from G, C, or T;

each N is independently selected from A, T, C, or G; and

each M is independently selected from A or C;

with the proviso that

at least 4 nucleotides of each -RGBNNM- group of nucleotides are identical with the nucleotides at comparable positions of the sequence -AGGTCA-; and

said second half-site is obtained from a glucocorticoid receptor subfamily response element.

15. A method according to claim 1 wherein said ligand is a naturally occurring ecdysone, an ecdysone-analog or an ecdysone mimic.

16. A method according to claim 15 wherein said naturally occurring ecdysone is α-ecdysone or β-ecdysone.

17. A method according to claim 15 wherein said ecdysone analog is ponasterone A, ponasterone B, ponasterone C, 26-iodoponasterone A, muristerone A, inokosterone or 26-mesylinokosterone.

18. A method according to claim 15 wherein said ecdysone mimic is 3,5-di-tert-butyl-4-hydroxy-N-isobutyl-benzamide, 8-O-acetylharpagide, a 1,2-diacyl hydrazine, an N'-substituted-N,N'-disubstituted hydrazine, a dibenzoylalkyl cyanohydrazine, an N-substituted-N-alkyl-N,N-diaroyl hydrazine, an N-substituted-N-acyl-N-alkyl, carbonyl hydrazine or an N-aroyl-N'-alkyl-N'-aroyl hydrazine.

19. (Amended) A method according to claim 1 wherein said exogenous gene is a wild type gene and/or gene of interest.

20. A method according to claim 19 wherein said wild type gene encodes products:

the substantial absence of which leads to the occurrence of a non-normal state in said cell; or

a substantial excess of which leads to the occurrence of a non-normal state in said cell.

21. (Amended) A method according to claim 19 wherein said gene of interest encodes products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to cells in which they are expressed.

22. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising an exogenous gene under the control of a response element to which the modified ecdysone receptor encoded by the DNA of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR);

(ii) DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified ecdysone receptor.

23. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of a response element to which a modified ecdysone receptor binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), said method comprising introducing into said cell:

a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said receptor, in combination with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, activating transcription therefrom.

24. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) a DNA construct encoding said recombinant product under the control of a response element to which the modified ecdysone receptor encoded by the DNA of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), and

(ii) DNA encoding a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived

from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified ecdysone receptor, and optionally a receptor capable of acting as a silent partner for said modified ecdysone receptor.

39. A method according to claim 13, wherein said first half-site is obtained from an ecdysone response element and said second half-site is obtained from a glucocorticoid response element, a mineralocorticoid response element, a progesterone response element or an androgen response element.

40. A method according to claim 39, wherein said second half-site is obtained from a glucocorticoid response element.

47. A method according to claim 1, wherein said receptor capable of acting as a silent partner is present.

48. A method according to claim 47 wherein said receptor capable of acting as a silent partner is ultraspiracle.

49. A method according to claim 1 wherein said modified ecdysone receptor has substantially no binding affinity for endogenous response elements.

50. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

51. (Amended) A method according to claim 50, wherein said receptor capable of acting as a silent partner is present.

52. (Amended) A method according to claim 51, wherein said receptor capable of acting as a silent partner is ultraspiracle.

53. A method according to claim 50, wherein said cell is a mammalian cell.

54. (Amended) A method according to claim 51, wherein said receptor capable of acting as a silent partner is RXR.

55. (Amended) A method according to claim 54, wherein said RXR is exogenous to said cell.

57. (Amended) A method according to claim 50 wherein said modified receptor is further characterized as having substantially no activity in mammalian cells.

58. (Amended) A method according to claim 50 wherein the DNA-binding domain of said modified receptor is derived from a member of the steroid/thyroid hormone superfamily of receptors.

59. (Amended) A method according to claim 50 wherein said activation domain is derived from a member of the steroid/thyroid hormone superfamily of receptors.

60. (Amended) A method according to claim 50 wherein said activation domain is a glucocorticoid receptor activation domain, a VP16 activation domain or a GAL4 activation domain.

61. A method according to claim 50, wherein said ecdysone response element has substantially no binding affinity for farnesoid X receptor (FXR).

62. A method according to claim 50 wherein said modified receptor has an altered DNA binding specificity relative to the wildtype receptor from which it is derived.

63. A method according to claim 50 wherein said modified receptor is present primarily in the form of a homodimer.

64. (Amended) A method according to claim 50 wherein said exogenous gene is a wild type gene and/or gene of interest.

65. A method according to claim 64 wherein said wild type gene encodes products:

the substantial absence of which leads to the occurrence of a non-normal state in said cell; or

a substantial excess of which leads to the occurrence of a non-normal state in said cell.

66. (Amended) A method according to claim 64 wherein said gene of interest encodes products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to cells in which they are expressed.

67. (Amended) A method of inducing the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said cell to conditions suitable to induce expression of said modified receptor.

68. (Amended) A method of inducing expression of an exogenous gene in an isolated cell containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said cell:

a modified receptor, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

wherein said modified receptor, in combination with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.

69. (Amended) A method for the expression of a recombinant product detrimental to isolated host cells, said method comprising:

transforming suitable isolated host cells with:

(i) a DNA construct encoding said recombinant product under the control of an ecdysone response element, and

(ii) DNA encoding a modified receptor, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

growing said host cells in suitable media; and

inducing expression of said recombinant product by introducing into said host cells one or more ligands for said modified receptor, and optionally a receptor capable of acting as a silent partner for said modified receptor.

70. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element wherein said modified receptor has substantially no constitutive activity in mammalian cells, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

71. (Amended) A method for modulating the expression of an exogenous gene in an isolated cell containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has an altered DNA binding specificity relative to the wildtype receptor from which it is derived, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to the cell an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in the cell; and wherein said one or more ligands are not toxic to said cell.

72. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising said exogenous gene under the control of a response element to which the modified ecdysone receptor of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR); and

(ii) a modified ecdysone receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an

ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to said subject an effective amount of one or more ligands for said modified ecdysone receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

73. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising an exogenous gene under the control of a response element to which the modified ecdysone receptor encoded by the DNA of (ii) binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR);

(ii) DNA encoding a modified ecdysone receptor under the control of an inducible promoter, wherein said modified ecdysone receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, and wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

(iii) one or more ligands for said modified ecdysone receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified ecdysone receptor.

74. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of a response element to which the modified ecdysone receptor described below binds, wherein said response element has substantially no binding affinity for farnesoid X receptor (FXR), said method comprising introducing into said subject:

a modified ecdysone receptor, wherein said modified ecdysone receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified ecdysone receptor,

wherein said modified ecdysone receptor, in combination with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, activating transcription therefrom.

75. (Amended) A method for modulating the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising said exogenous gene under the control of an ecdysone response element; and

(ii) a modified receptor which, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription

factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

said method comprising providing to said subject an effective amount of one or more ligands for said modified receptor; wherein said one or more ligands are not normally present in said subject; and wherein said one or more ligands are not toxic to said subject.

76. (Amended) A method of inducing the expression of an exogenous gene in a mammalian subject containing:

(i) a DNA construct comprising an exogenous gene under the control of an ecdysone response element,

(ii) DNA encoding a modified receptor under the control of an inducible promoter, wherein said modified receptor, in the presence of a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein;

(iii) one or more ligands for said modified receptor;

said method comprising subjecting said subject to conditions suitable to induce expression of said modified receptor.

77. (Amended) A method of inducing expression of an exogenous gene in a mammalian subject containing a DNA construct containing said exogenous gene under the control of an ecdysone response element, said method comprising introducing into said subject:

a modified receptor, wherein said modified receptor has substantially no binding affinity for endogenous response elements, and wherein said modified receptor comprises: (a) a ligand binding domain capable of binding an ecdysteroid; (b) a DNA-binding domain derived from a DNA-binding protein, wherein said DNA-binding domain has substantially no binding affinity for endogenous response elements; and (c) an activation domain of a transcription factor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or an E. coli LexA protein; and

one or more ligands for said modified receptor,

wherein said modified receptor, in connection with a ligand therefor, and optionally in the further presence of a receptor capable of acting as a silent partner therefor, binds to said ecdysone response element, activating transcription therefrom.